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RESEARCH ARTICLE

Anti-Hyperglycemic, Anti-Hyperlipidemic and Antioxidant Potential of Alcoholic-Extract of *Sida cordifolia* (Areal Part) in Streptozotocin-Induced-Diabetes in Wistar-Rats

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Abstract *Sida cordifolia* is a shrub found throughout the tropical and sub-tropical plains. All parts of the plant are used as anti-rheumatic, antipyretic, anti-asthmatic, laxative, diuretic, vasorelaxative, hypotensive, central nervous system depressant, antioxidant, analgesic and hypoglycemic. The present study was aimed to evaluate the hypoglycemic, anti-hyperlipidemic and antioxidant potential of alcoholic-extract obtained from areal part of *S. cordifolia* in streptozotocin-induced-diabetes in wistar-rats. Diabetes was induced with streptozotocin at the intra-peritoneal dose of 55 mg/kg. Diabetic rats were treated with alcoholic extract of *S. cordifolia* at dosage of 200, 400 mg/kg and glibenclamide (5 mg/kg) after sub-acute administration for 28 days. Alcoholic extract of *S. cordifolia* at 400 mg/kg significantly improved the body-weight whereas significantly decreased the blood glucose level in diabetic rats. However at 400 mg/kg, the alcoholic extract of *S. cordifolia* showed beneficial effect indicating significant decrease in total cholesterol, triglycerides, low density lipids, plasma-creatinine, plasma-urea nitrogen and lipid-peroxidation and a significant increase in high density lipid-level in diabetic rats. Interestingly at 400 mg/kg, a significant increase in antioxidant enzymes such as catalase and superoxide-dismutase-activity was seen in the diabetic rats. The dose 200 mg/kg of alcoholic extract of *S. cordifolia* showed non-significant change in diabetic rats. The above therapeutic-potential of alcoholic extract of areal parts of plant may be because of the presence of bioactive compounds such as glycosides, resins, alkaloids, sterols, saponins and flavonoids. Thus, the findings of the present study indicate that the alcoholic extract of *S. cordifolia* at dosage level of 400 mg/kg produces anti-diabetic effect in the streptozotocin-induced diabetes in wistar-rats.

Keywords *Sida cordifolia* · Alcoholic-extract · Anti-diabetic · Streptozotocin · Wistar-rats

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Introduction

Diabetes mellitus (DM) is the most common endocrine disorder characterized by hyperglycemia resulting from defects either in insulin secretion or insulin action or both [1, 2]. Diabetes is the third killer disease of mankind after cancer and cardiovascular diseases because of its high prevalence, morbidity and mortality [3]. The efficiency of defense mechanism of body is altered in diabetes which results in ineffective scavenging of free radicals and therefore results in tissue damage [4].

To control the disease, several conventional-drugs are available along with insulin but their prolonged use may lead to other complications like blurred vision, hypoglycemia and a lingering condition like coma [5, 6]. The anti-diabetic-drugs such as modern oral hypoglycemic agents' like sulphonyl-ureas (tolbutamide, glibenclamide) and insulin-sensitizer (troglitazone) are associated with various side effects [6]. To reduce its damaging property it is better to use conventional-drugs along with hypoglycemic-herbs [7]. More than 800 plants possess anti-diabetic activity [8,

9]. *Sida cordifolia* (Linn.) a shrub belonging to the family Malvaceae, improves the diabetic conditions [10, 11]. It is found through out the tropical and sub tropical plains of India. Its roots, leaves, stem and seeds are used in the folk medicine as anti-rheumatic [12], antipyretic [13], anti-asthmatic [14], laxative, diuretic [12, 15, 16], vaso-relaxative [17], hypotensive [14], CNS depressant [18, 19], antioxidant [20] and hypoglycemic effect [21, 22]. Keeping the fact that diabetes is an emerging problem world-wide and is a major concern of developing countries like India; the present study was conducted with the aim to evaluate the anti-oxidative and anti-diabetic activity of *S. cordifolia* in streptozotocin (STZ) induced diabetes in wistar rats.

Material and Methods

Collection and Extraction of Plant Materials

The areal parts of the plant *S. cordifolia* were collected and after authentication plant material was chopped into small pieces and kept under shade for drying (30–35 °C). The plant material was pulverized to powder form with mixer-grinder and subjected to alcoholic extraction in soxhlet-apparatus [23] and its % extractability was determined [24]. The presence of phyto-chemicals in the extract such as alkaloids [25], glycosides [26], saponins [27], sterols [28], resins [29] and flavonoids [30] were determined.

Experimental Animals

The experimental protocol was duly approved by institutional ethics committee. The study was conducted on healthy wistar rats of either sex weighing 170–230 g, procured from Indian Institute of Integrative Medicine (IIIM Lab), Jammu, India. The animals were provided standard pelleted ration and *ad libitum* drinking tap water. Prior to the start of the experiment, the rats were acclimatized in the laboratory conditions for a period of more than 3 weeks. A daily cycle of 12 h of light and 12 h of darkness was provided to animals.

Induction of Diabetes

Streptozotocin solution (0.5 %) was freshly prepared in ice cold sodium citrate buffer (0.1 M; pH 4.5) in a volume of 10 mg/ml and administered to overnight fasted wistar-rats intra-peritoneally at the dose of 55 mg kg^{-1} body-weight [31–33]. The rats were kept only on glucose solution (5 %) in drinking water for next 24 h after the STZ administration to prevent hypoglycemia [34, 35]. To declare that the rats became diabetic, after 72 h of STZ administration the biomarker of blood glucose level [36] was determined by using glucometer (Accu-Check, Roche, Germany) and rats showing more than 200 mg/dl blood glucose level were considered as the diabetic rats [37].

Experimental Design

A total of 30 healthy-wistar rats were selected and divided into five-groups containing six animals in each group. Diabetes was induced in rats of group II, III, IV and V whereas group I served as control. The diabetic rats of group II acted as diabetic control only treated with carboxy-methyl-cellulose (1 %) whereas groups III and IV diabetic rats were treated with alcoholic extract of *S. cordifolia* at dosage of 200 and 400 mg/kg after mixing in carboxy-methyl-cellulose (1 %) for 28 days, respectively. Group V diabetic rats received glibenclamide at dosage of 5 mg/kg orally for 28 days. Blood samples of about 2–4 ml were collected from retro-orbital sinus of wistar-rats under inhalational anesthesia on day 0, 15 and 29 using capillary-tubes and the blood glucose level was measured at the time of sample collection. The blood samples were centrifuged at 3,000 rpm for 15 min to harvest the plasma which was kept in clean sterile glass test tubes at −20 °C for further biochemical analysis. The sediment left after taking out the plasma, from which WBC buffy-coat was removed. The left-over erythrocyte sediment was then washed 2–3 times and diluted with gentle pouring of normal saline solution in the ratio of 1:1 on v/v basis and thoroughly mixed with erythrocyte sediment to make 1 % and 33 % hemolysate used for the estimation of anti-oxidant-enzymes (catalase, superoxide-dismutase) and lipid-peroxidation (LPO) respectively.

Biochemical and Oxidative Stress Parameters and Body Weight of the Animals

Biochemical indices such as blood glucose, triglycerides, cholesterol, high density lipoproteins (HDL), plasma urea nitrogen and plasma creatinine were assayed on day 0 (pretreatment), day 15 and day 29 (post treatment) using kits (Erba, HP, India). However, low density lipoprotein (LDL) in plasma was estimated using the following formula [38].

$$\mathrm{LDL\ (mg/dl)} = \mathrm{TC} - \mathrm{HDL} - \mathrm{TG}/5.0,$$

where TC is the total cholesterol and TG is the triglycerides

To detect any changes in body weight the animals were weighed. The antioxidant enzymes superoxide dismutase (SOD) [39], catalase [40] and tissue damage biomarker LPO [41] were estimated in blood samples.

Statistical Analysis

Statistical data analysis was done using analysis of variance (ANOVA) which was carried out in completely randomized design (CRD) and the significance was tested using Duncan Multiple Range Test [42] and the level of significance was assayed at 5 % level ($P < 0.05$).

Results and Discussion

The percent alcoholic extractability of *S. cordifolia* was 19.06 % (w/w) and extract revealed the presence of alkaloids, glycosides, saponins, sterols, resins, fixed oil and flavonoids. Kaur et al. [43] also reported similar percent extractability. The findings of phytochemicals were similar to the findings of Ghosal et al. [44], Guntilaka et al. [45], Kapoor [46], Sutradhar et al. [47], and Pawar et al. [48].

A significant increase in blood glucose level was observed in group II, III, IV and V diabetic rats on day 0 as compared to group I control rats (Fig. 1). Treatment was given to group IV diabetic rats with alcoholic extract of *S. cordifolia* at the dose of 400 mg/kg which produced a significant decrease in blood glucose level on day 15 and 29 as compared to day 0. The blood glucose level in group IV and group V on day 29 decreased to the extent which is comparable to control rats of group I, but the dose 200 mg/kg was not enough to decrease blood glucose level appreciably in group III diabetic rats. Although with glibenclamide treatment, the blood glucose level in group V diabetic rats was significantly decreased and was comparable to group I control rats. Similar decrease in blood glucose level was also reported at different doses of *S. cordifolia* [15, 21, 43]. The possible mechanism of hypoglycemic activity of *S. cordifolia* may be through increase in glucose metabolism [43]. It has been reported that mainly alkaloids and flavonoids are responsible for an increase in insulin secretion and peripheral glucose utilization [49].

Diabetes is characterized with the loss of body weight as body protein or fats are being utilized for energy generation through gluconeogenesis [50]. A significant decrease in body weight was found in diabetic rats of group II on day 0 and 29 as compared to rats before diabetic (pretreatment) within same group while in *S. cordifolia* (400 mg/kg) and glibenclamide treated diabetic rats of group IV and V, a significant increase in body weight was found on day 29 as compared to day 0 within the same group, respectively (Fig. 2). Although the dosage of *S. cordifolia* (200 mg/kg) used for diabetic rats of group III was not sufficient to check the decrease in body weight on day 29 as compared to day 0. A significant improvement in body weight of diabetic rats indicated the possible role of extract in restoration of protein metabolism which is supported by Kaur et al. [43]. The ability of plant extract in restoration of body weight of diabetic rats may be through reversal of gluconeogenesis [51].

A significant decrease in triglyceride (Fig. 3), LDL (Fig. 4) and cholesterol levels (Fig. 5) were found on day 15 and 29 in group IV and V diabetic rats treated with plant extract at dose 400 mg/kg and glibenclamide as compared to day 0 within the group, respectively and also comparable to control rats on day 29. While the dose 200 mg/kg of *S. cordifolia* given to group III diabetic rats showed non significant change in triglyceride and cholesterol level on day 29 as compared to day 0.

A significant increase in HDL level was observed in group IV and group V diabetic rats treated with plant extract at dose 400 mg/kg and glibenclamide on day 15 and 29 as compared to day 0, respectively and comparable to control rats on day 0 (Fig. 6). Although HDL level showed non-significant change in group III diabetic rats treated at 200 mg/kg of plant-extract as compared to day 0. Diabetes affects the fat management indicated by an increase in total cholesterol, triglycerides and LDL, with decrease in HDL levels [52–54]. Similarly, Kaur et al. [43] also reported ameliorative effect with aqueous extract of *S. cordifolia* at the dose of 1,000 mg/kg. The hypo cholesterolemic effect of the plant may be due to overall inhibition of fatty acid synthesis [43, 55]. The significant reduction of LDL levels, in *S. cordifolia* treated rats may be due to the activation of LDL receptors in hepatocytes thus reducing the serum LDL level or may be due to the inhibition of cholesterol synthesis pathway [56]. The effect of *S. cordifolia* extract to decrease triglycerides may be through increase of insulin levels. Insulin activates the enzyme lipoprotein lipase and hydrolyses triglycerides and the deficiency in insulin, thereby causes hyper triglyceridemia [43].

The diabetic hyperglycemia induces elevations of blood creatinine and urea levels which are considered as significant markers of renal dysfunction. A significant decrease in plasma-urea-nitrogen (Fig. 7) and plasma creatinine (Fig. 8) levels was observed on day 29 as compared to day 0 in group IV diabetic rats treated with plant extract at 400 mg/kg and also comparable to control rats of group I. Although the dose 200 mg/kg for group III diabetic rats showed non significant change in plasma urea nitrogen and plasma creatinine levels on day 29. However in group V glibenclamide treated diabetic rats on day 29 a significant decrease in plasma-urea-nitrogen and plasma-creatinine levels was found as compared to day 0 which is comparable to group I control rats. Similar to present findings, Makwana et al. [57] reported that the aqueous extract of *S. cordifolia* has nephro protective potential in nephrotoxicity induced by gentamicin and cisplatin. The higher amount of glucose in blood makes the kidney to work more which

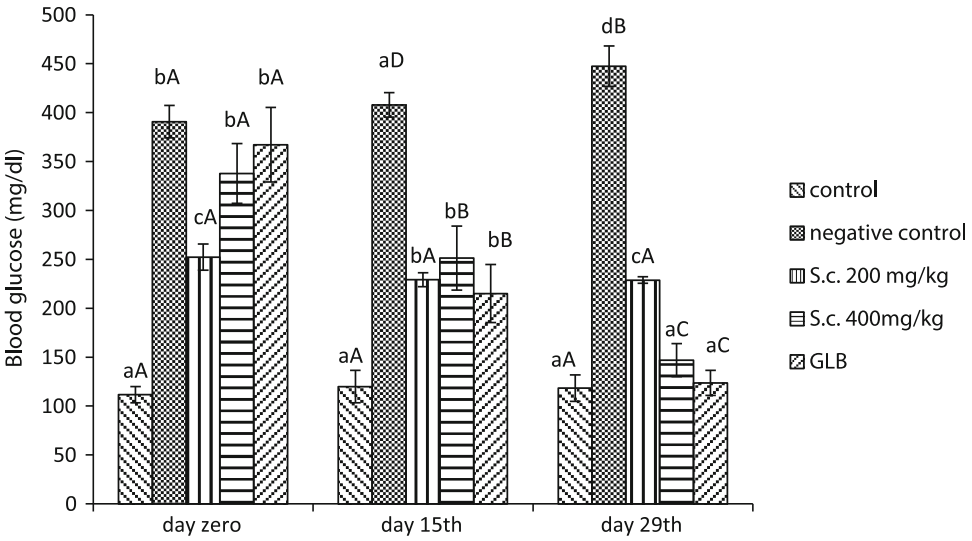

Fig. 1 Effect of alcoholic-extract of *S. cordifolia* and glibenclamide on blood glucose level after oral administration in diabetic wistar-rats ($n = 6$). *Capital superscript* (*alphabet*) indicates level of significance within the group. *Small superscript* (*alphabet*) indicates level of significance between the groups

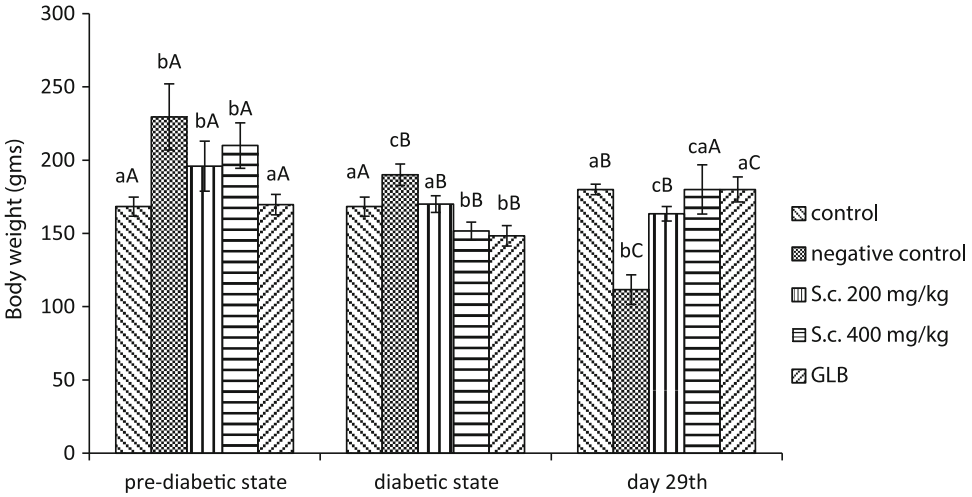

Fig. 2 Effect of alcoholic-extract of *S. cordifolia* and glibenclamide on body-weight after oral administration in diabetic wistar-rats ($n = 6$). *Capital superscript* (*alphabet*) indicates level of significance within the group. *Small superscript* (*alphabet*) indicates level of significance between the groups

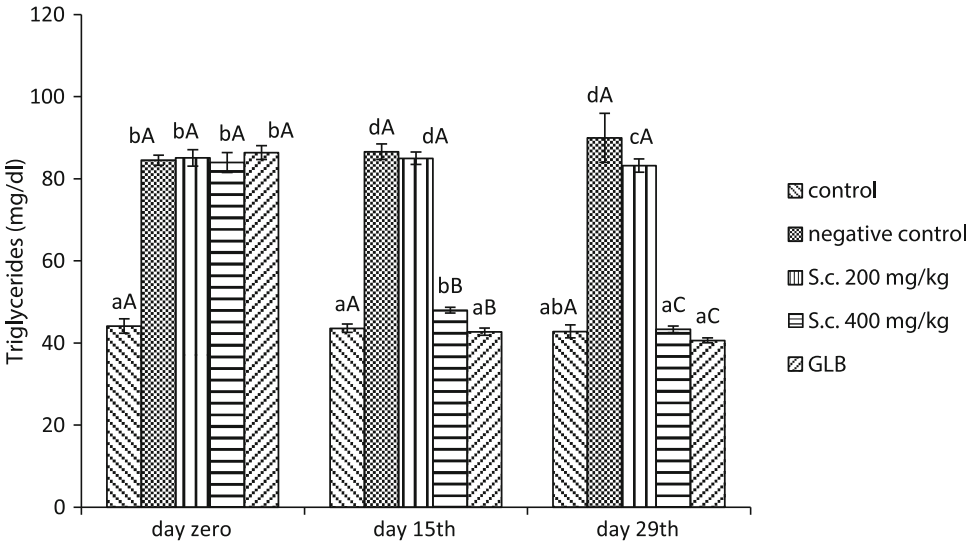

Fig. 3 Effect of alcoholic-extract of *S. cordifolia* and glibenclamide on triglyceride after oral administration in diabetic wistar-rats ($n = 6$). *Capital superscript* (*alphabet*) indicates level of significance within the group. *Small superscript* (*alphabet*) indicates level of significance between the groups

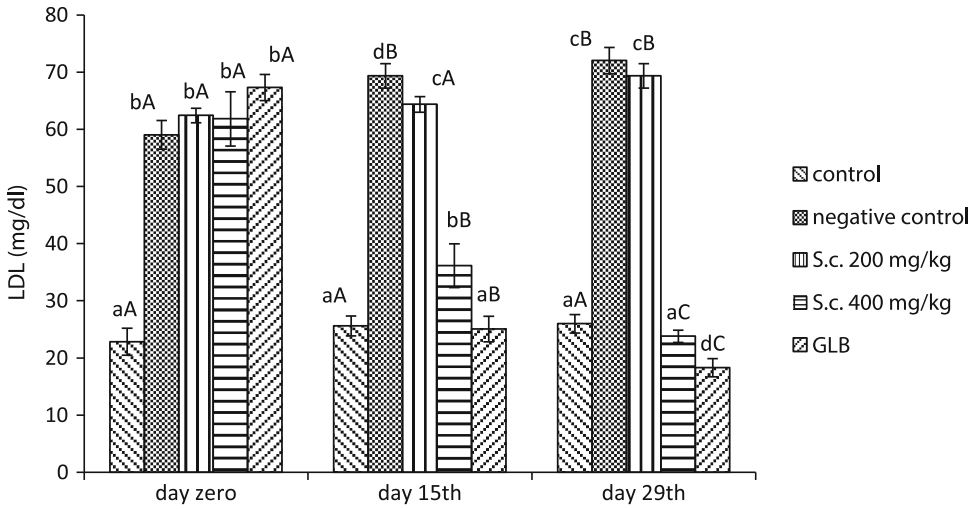

Fig. 4 Effect of alcoholic-extract of *S. cordifolia* and glibenclamide on LDL levels after oral administration in diabetic wistar-rats ($n = 6$). *Capital superscript* (*alphabet*) indicates level of significance within the group. *Small superscript* (*alphabet*) indicates level of significance between the groups

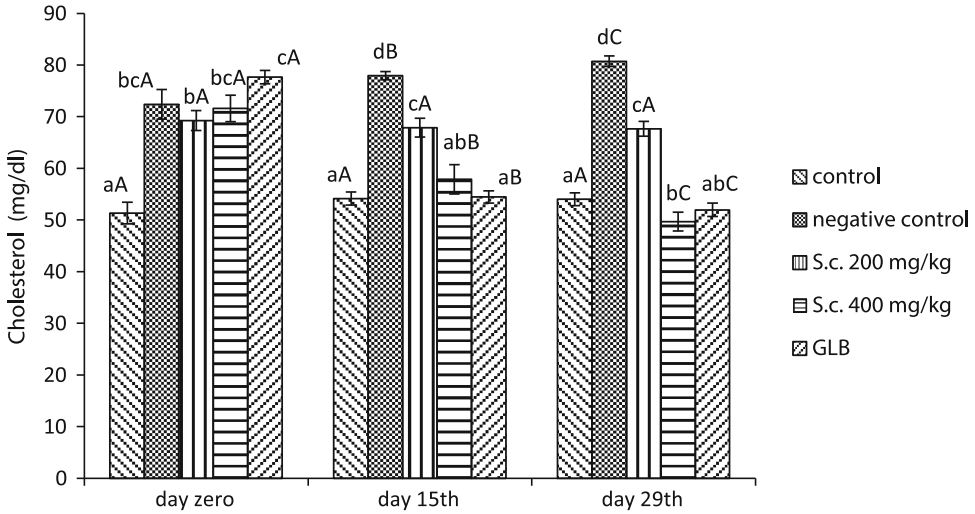

Fig. 5 Effect of alcoholic-extract of *S. cordifolia* and glibenclamide on cholesterol level after oral administration in diabetic wistar-rats ($n = 6$). *Capital superscript* (*alphabet*) indicates level of significance within the group. *Small superscript* (*alphabet*) indicates level of significance between the groups

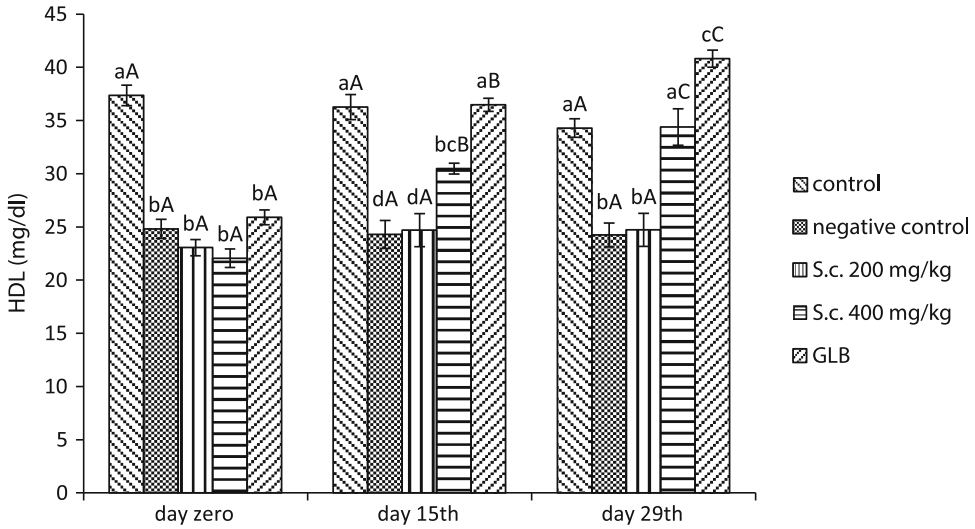

Fig. 6 Effect of alcoholic-extract of *S. cordifolia* and glibenclamide on HDL level after oral administration in diabetic wistar-rats ($n = 6$). *Capital superscript* (*alphabet*) indicates level of significance within the group. *Small superscript* (*alphabet*) indicates level of significance between the groups

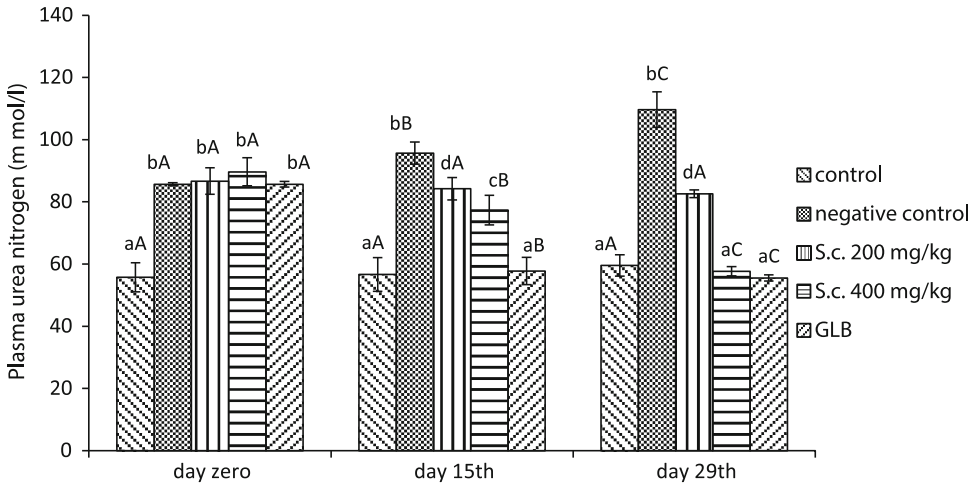

Fig. 7 Effect of alcoholic-extract of *S. cordifolia* and glibenclamide on plasma urea nitrogen after oral administration in diabetic wistar-rats ($n = 6$). *Capital superscript* (*alphabet*) indicates level of significance within the group. *Small superscript* (*alphabet*) indicates level of significance between the groups

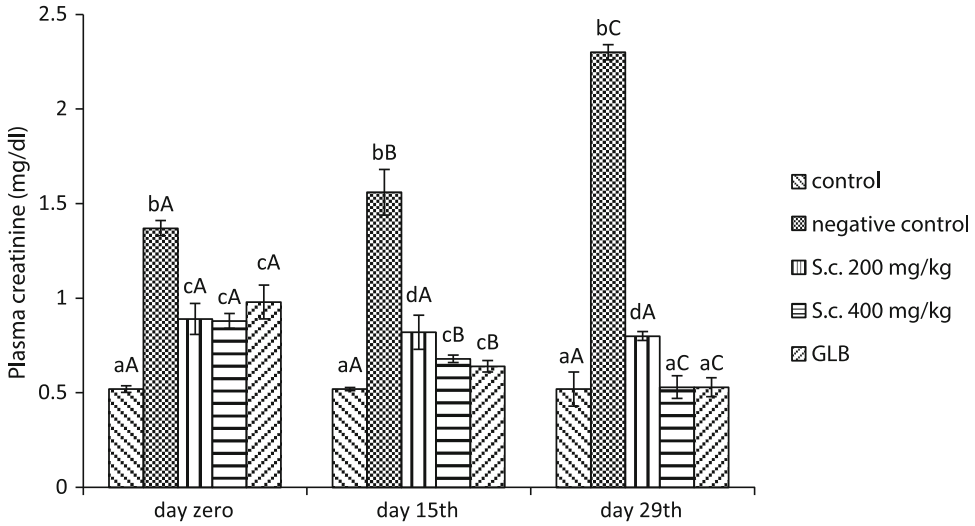

Fig. 8 Effect of alcoholic-extract of *S. cordifolia* and glibenclamide on plasma creatinine after oral administration in diabetic wistar-rats ($n = 6$). *Capital superscript* (*alphabet*) indicates level of significance within the group. *Small superscript* (*alphabet*) indicates level of significance between the groups

results in more waste product formation indicated by an increase in the serum-creatinine and BUN level [58, 59]. *Sida cordifolia* might have exhibited nephron protective activity by virtue of its antioxidant potential [57].

Oxidative stress in diabetes co-exists with the decrease in antioxidant status, thus increasing the deleterious effects of free radicals. In hyperglycemia, glucose undergoes auto-oxidation which in turn leads to peroxidation of lipids in lipoproteins. A significant decrease in LPO was found on day 29 in group IV and group V diabetes rats treated with plant extract at 400 mg/kg and glibenclamide as compared to day 0 within same group, respectively (Fig. 9). Although group III treated diabetic rats at dose 200 mg/kg of *S. cordifolia* non-significantly decreases the LPO on day 29 as compared to day 0. It is well known that MDA is a terminal product of LPO, thus the concentration of MDA can disclose the extent of LPO in diabetes [60–62]. The reactive oxygen species (ROS) take electrons from polyunsaturated fatty acids of cell membrane which leads to LPO with the loss of cellular functions [63]. Dhalwal et al. [20] reported that extracts from root of *S. cordifolia* scavenges the free-radical and possess antioxidant-activity. Auddy et al. [64] also reported the *in vivo* and *in vitro* antioxidant activity of whole plant of *S. cordifolia.*

A significant increase in catalase (Fig. 10) and SOD (Fig. 11) activities were found in group IV and group V diabetes-rats treated with plant extract at dose 400 mg/kg and glibenclamide on day 29 as compared to day 0 respectively and enzymes activities were comparable to control rats of group I. Although the dose 200 mg/kg, non-significant changes in antioxidant enzymes (SOD and CAT) were found in group III diabetic rats on day 29 as compared to day 0. Antioxidant enzymes such as SOD and catalase play a very vital role in alleviating the free-radicals oxidative-stress in diabetes. SOD protects from toxic effect of ROS by scavenging superoxide-ions and yielding less reactive hydrogen peroxides [65]. Catalase, a heme protein catalyses the reduction of hydrogen peroxide and protects the tissue from highly reactive hydroxyl radicals [66, 67]. Similar anti-oxidant property of *S. cordifolia* has

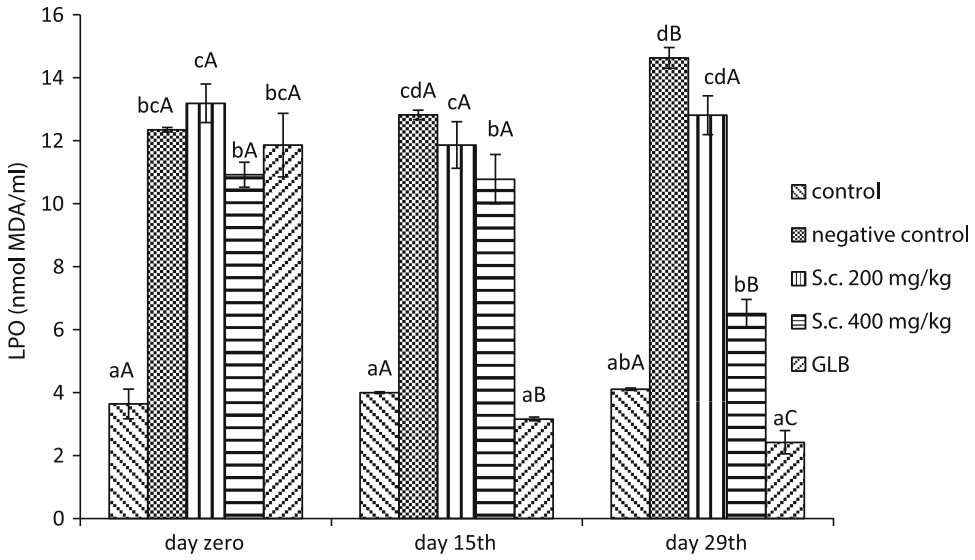

Fig. 9 Effect of alcoholic-extract of *S. cordifolia* and glibenclamide on LPO after oral administration in diabetic wistar-rats ($n = 6$). *Capital superscript* (*alphabet*) indicates level of significance within the group. *Small superscript* (*alphabet*) indicates level of significance between the groups

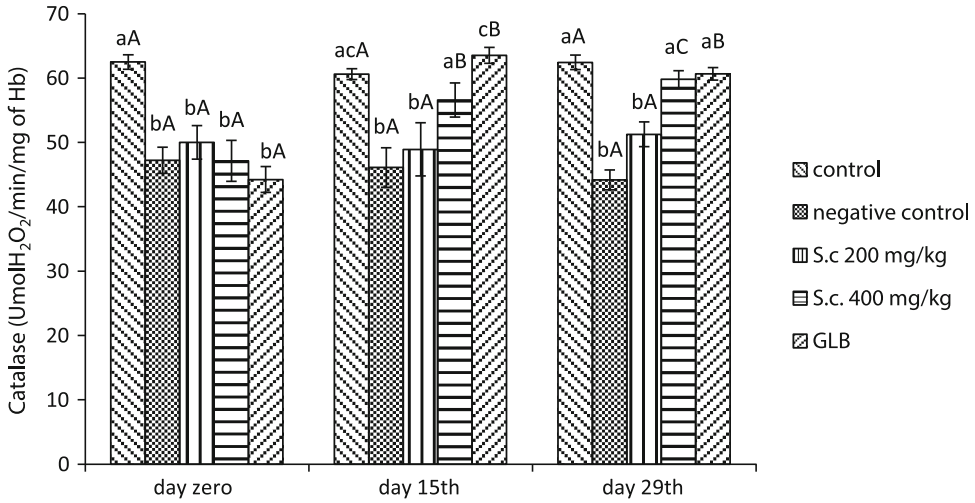

Fig. 10 Effect of alcoholic-extract of *S. cordifolia* and glibenclamide on antioxidant enzyme catalase activity after oral administration in diabetic wistar-rats ($n = 6$). *Capital superscript* (*alphabet*) indicates level of significance within the group. *Small superscript* (*alphabet*) indicates level of significance between the groups

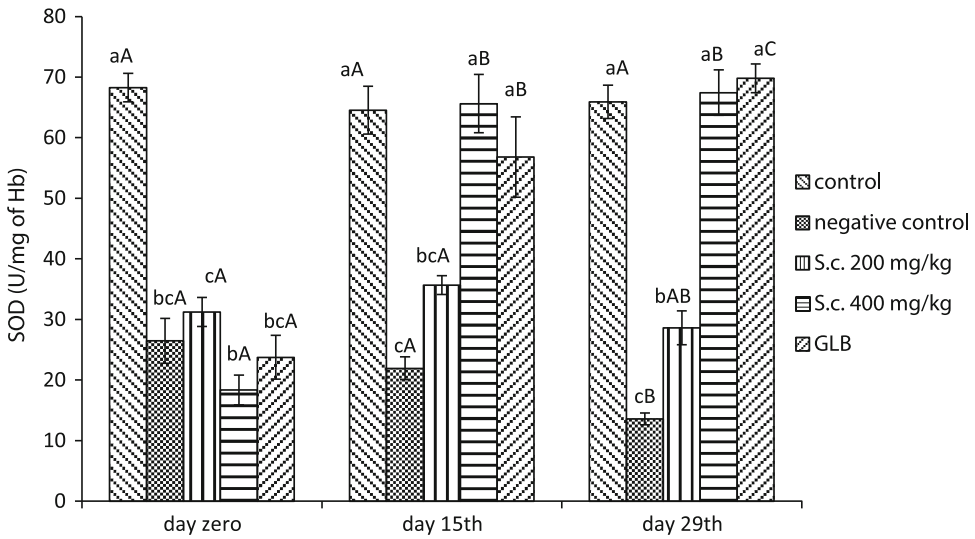

Fig. 11 Effect of alcoholic-extract of *S. cordifolia* and glibenclamide on antioxidant enzyme SOD activity after oral administration in diabetic wistar-rats ($n = 6$). *Capital superscript* (*alphabet*) indicates level of significance within the group. *Small superscript* (*alphabet*) indicates level of significance between the groups

also been correlated with findings of Pawar et al. [48]. Therefore oxidative stress increases the level of LPO [68] and decrease SOD and catalase levels [60, 61, 69, 70].

Sida cordifolia is considered safe as far as its toxicity potential is concerned. As per the literature its LD_{50} is more than 3 g/kg [71], thus *S. cordifolia* can be used safely in medicinal practices without causing any toxicity.

Conclusion

Alcoholic extract of *S. cordifolia* at the dose of 400 mg/kg showed a significant increase in antioxidant enzymes such as catalase and superoxide dismutase levels and significant decrease in LPO in STZ induced diabetes in wistar rats within a treatment period of 28 days. However, no such findings have been found in alcoholic extracts of *S. cordifolia* at dosage level of 200 mg/kg.

Based on the data of present study, it is concluded that alcoholic extract of *S. cordifolia* at a dose of 400 mg/kg have potency to act as anti diabetic, hypoglycemic and anti oxidant properties and also helps to check muscle wasting. Further it also protects from LPO that damages the cell membrane. The above therapeutic potential of the extract from areal part of plants could be due to the presence of bioactive compounds such as glycosides, resins, alkaloids, sterols, saponins, flavanoids etc.

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